REMARKS

Favorable consideration of the subject application is respectfully requested in view of the above amendments and the following remarks. This reply is being filed within the shortened three-month statutory period, and no extension of time or fee is therefore required.

Following entry of the above amendments, claims 21, 23-31, 33, 35, 36 and 37-45 are pending in the application, with claims 21, 35, 38, and 45 being in independent format.

Amendments

Claim 21 is amended to recite a method for treating migraine headaches, cortical spreading depression and symptoms of such conditions. The method comprises administering an effective amount of a $Na^+K^+2Cl^-$ cotransporter antagonist to the central nervous system of the subject being treated.

Claim 22 is believed to be unnecessary in view of the amendment to claim 21, and is therefore cancelled, in view of the amendment to claim 21.

Claim 23 is amended to be consistent with claim 21.

Claim 27 is amended to depend from claim 23 and to recite that the loop diuretic is selected from furosemide and furosemide-related compositions, and to remove thiazides and thiazide-like compositions from the claim.

Claim 28 is amended to depend from claim 27 and to recite anticonvulsants and non-steroidal anti-inflammatory drugs as preferred additionally administered agents.

Claim 29 is amended to depend from claim 28 and recites a preferred anticonvulsant agent (i.e., divalproex sodium).

Claim 30 is amended to refer to the $Na^+K^+2Cl^-$ cotransporter antagonist (instead of the treatment composition).

Claim 31 is amended to refer to the $Na^+K^+2Cl^-$ cotransporter antagonist (instead of the treatment composition).

Claim 32 is cancelled in view of the cancellation of claim 22, from which this claim depended.

Claim 34 is cancelled in view of the amendment to claim 27.

Claim 35 is amended to recite a method for treating cortical spreading depression and migraine symptoms in a human in need of such treatment. The method comprises selecting a $Na^+K^+2Cl^-$ cotransporter antagonist based on its ability to inhibit synchronized population

discharges of neuronal populations in the CNS of a mammal without decreasing excitatory synaptic transmission, and administering the antagonist to the central nervous system of said human in an amount that is effective in ameliorating or aborting said symptoms.

Claim 36 is amended to recite that the antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system.

Claim 37 is amended to refer to the $Na^+K^+2Cl^-$ cotransporter antagonist of claim 35(instead of the treatment composition).

Claim 38 is amended to recite a method for treating a patient who suffers from migraine headaches, cortical spreading depression and premonitory symptoms of migraine headache. The method comprises administering an effective therapeutic amount of a loop diuretic selected from furosemide or a furosemide-related composition to the patient wherein the symptoms are ameliorated by the treatment.

Claims 41 and 42 are new claims which recite that the loop diuretic is administered intranasally.

Claims 43 and 44 are new claims which recite that the loop diuretic is administered directly into the cerebrospinal fluid.

Claim 45 is a new claim reciting treating migraine headaches with a cation chloride cotransporter antagonist to the central nervous system of the subject.

It is believed that all of the amended and new claims are fully supported by the specification as originally filed and that no new matter has been added. The amendment to claim 36 is specifically supported in the present application and all prior applications relied upon for priority (see, e.g., Figs 2L and 2R in U.S. Patent No. 6,495,601 and corresponding Examples).

Rejections

Rejection under 35 USC §112, first paragraph (enablement)

Claims 21-34 stand rejected under 35 USC §112, first paragraph . The Office Action stated that the specification was enabling for treatment of migraine headache, cortical spreading depression and symptoms of migraine headache such as "visual aura" but lacked sufficient enablement for methods of prevention of migraine headaches, cortical spreading depression and other headache conditions. The Examiner interpreted prevention as meaning "cure or total eradication" (see "**State of the Art**", page 3 of the Office Action).

In addition, while the Office Action acknowledged that the specification is enabling for loop diuretics such as furosemide and furosemide-related compositions, certain methods were said not to be enabled, e.g., methods reciting "a treatment composition having ion-dependent cotransporter antagonist activity", "the treatment composition comprises a loop diuretic", "thiazides and thiazide-like compositions", "the treatment composition has cation chloride cotransporter antagonist activity", "the treatment composition has glial cell $Na^+K^+2Cl^-$ cotransporter antagonist activity", and "a treatment composition that modulates the synchronization of neuronal discharges in the central nervous system" (Office Action, section 4, page 5)

This rejection is addressed herein by the claim amendments and the remarks which follow.

The amended claim preambles omit mention of "a method of preventing" and "other headache conditions". The claims now recite "a method of treating" migraine headaches, cortical spreading depression and symptoms of such conditions.

It should be understood, however, that the applicant intended "a method of preventing" to mean prophylactic treatment, not a cure or eradication. It is clear that migraine prophylaxis is an accepted therapeutic approach to aborting migraine attacks in patients who are predisposed to this condition (see ,e.g. Mathew et al. (1996) cited in the Office Action, and other references provided by the Examiner). The efficacy of a prophylactic therapy can be assessed by objective criteria following administration of the therapy. Therefore, in deleting the word "preventing" from the claims, the applicant does not intend to surrender a method for prophylactic treatment.

The amended claims recite "$Na^+K^+2Cl^-$ cotransporter antagonist" to more clearly delineate that a suitable antagonist for use in the claimed treatment methods will exhibit this type of ion-dependent cotransporter antagonist activity. It should be understood from the specification that a $Na^+K^+2Cl^-$ cotransporter antagonist may possess additional cation chloride cotransport antagonist activities, and that the use of the antagonist may inherently affect other cation chloride cotransporters. The amendment to claim 23 recites loop diuretics, which are a subclass of $Na^+K^+2Cl^-$ cotransporter antagonists (see, e.g., standard pharmacology texts such as Goodman & Gilman).

It is believed that compounds that inhibit $Na^+K^+2Cl^-$ cotransporters are well known to those skilled in the art. In addition, assays for $Na^+K^+2Cl^-$ cotransporter antagonist activity (and loop diuretic activity) are well-known in the art and are routinely included in drug discovery

screens. These assays can be performed by technicians without undue experimentation. See also, disclosure in applicant's specification, page 23, line 12 et seq. The methods and Examples in the specification provide enablement for identifying a $Na^+K^+2Cl^-$ cotransporter antagonist that inhibits synchronization of neuronal discharges in the central nervous system. These methods, such as the use of extracellular and intracellular electrophysiological measurements in brain slices and in animal models are routinely used by those skilled in the art and do not require undue experimentation. The use of ion-selective electrodes to measure ion concentrations in extracellular fluid is also routine and well known to those skilled in the art.

Amended claim 35 includes the step of selecting a $Na^+K^+2Cl^-$ cotransporter antagonist for properties that are predictive of activity in treating cortical spreading depression and migraine symptoms and are enabled by methods in the specification, using furosemide as an example.

The applicant believes that sufficient guidance is provided in the specification and by knowledge in the art to enable the invention as presently claimed. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 USC §112, first paragraph (written description)

Claims 21-40 stand rejected under 35 U.S.C. §112, first paragraph, on grounds of written description. In particular, the Office Action indicates that the written description is satisfied for treatment of migraine headache, cortical spreading depression and "visual auras" of migraine, but the specification provides insufficient written description to support the genus of "other headache conditions and symptoms of such conditions" (see Office Action at bottom of page 12)..

It is believed that the rejection is obviated by the claim amendments, specifically, the removal of the phrase- "other headache conditions and symptoms of such conditions"- from the claims.

The applicant wishes to point out that, in addition to the disclosures referred to in the third paragraph of page 11 of the Office Action, the written description of the subject application provides Examples which teach, *inter alia,* that prolonged exposure to furosemide blocks spontaneous synchronized population discharges and induces negative field shifts, and inhibits depolarizing oscillations of extracellular field potentials induced in hippocampal slices by high potassium-low chloride medium. These teachings form the underpinnings of the claimed embodiments disclosed in the subject specification.

The applicant also respectfully points out that the specification discloses premonitory symptoms of migraine, such as visual, sensory, speech or motor symptoms, which are included in "migraine with aura", which are encompassed in the claimed methods of treatment. See, e.g., page 4, lines 20-22.

In view of the above amendments and remarks, the applicant respectfully requests the Examiner to withdraw this ground of rejection.

Rejection under 35 USC §112, second paragraph

Claims 21-40 stand rejected under 35 USC §112, second paragraph, as being indefinite. In particular, the Office Action points out that claims 21, 35 and 38 are directed to a method of preventing or treating "other headache conditions", which term is not defined in the specification.

It is believed that this rejection is obviated by the amendments of these claims. Accordingly, the applicant respectively requests the Examiner to withdraw this ground of rejection.

Rejections under 35 USC §102(b)

Claims 21-23, 25-27, 30-33 and 35-40 stand rejected under 35 USC § 102(b) as being anticipated by Read et al (Cephalalgia, 1997, December, 17☹8): 826-832. The Office Action cites this reference as teaching the use of furosemide in saline solution to inhibit regenerative cortical spreading depression in anesthetized cats. Specifically, the reference discloses that pretreatment of anesthetized cats with furosemide, prior to initiation of spreading depression by application of solid KCl to the cortex, produced a dose-dependent decrease in the number of dc negative potential shifts and in the total duration of spreading depression activity.

The applicant submits that this rejection is improperly lodged insofar as the reference was not publicly available more than a year before the filing of applicant's US Provisional Application No. 60/113,620 on December 23, 1998, to which the subject application claims benefit of priority. The applicant submits herewith date-stamped pages of the cited reference from Duke University Medical Library and from Thomas Jefferson University Library, showing that the reference was not publicly available prior to January 6, 1998. Accordingly, the applicant believes that this ground of rejection can be properly withdrawn.

Claims 21-24, 27-32 and 35-38 stand rejected under 35 U.S.C. 102(b) as being anticipated by Mathew et al. (Neurology 46: 1226-1230, 1996). The Office Action cites the reference as teaching the use of acetozolamide and furosemide in combination with abortive antimigraine agents (e.g., ergotamine, DHE, or sumatriptan) and prophylactic agents such as beta blockers, amitriptyline or methysergide for the treatment of chronic daily headache including migraine.

More specifically, as disclosed in applicant's specification at page 5, lines 16-21, and in the reference at page 1229, left-column, Mathew studied patients with refractory transformed migraine type of chronic daily headache (CDH), and showed that a subset of these patients who were treated after diagnosis of increased intracranial pressure with a combination of antimigraine agents, and acetazolamide and furosemide to reduce increased intracranial pressure, showed reduced number of days of severe headache, reduced consumption of abortive agents and overall improvement of quality of life.

It is believed that this rejection is obviated by the amendment of claims 21, 28, 29, 35 and 38.

In view of the above remarks and claim amendments, the applicant respectfully requests the Examiner to withdraw this ground of rejection.

Conclusion

In view of the above amendments and remarks, it is believed that the applicant has addressed the claim rejections, and that the claims now pending are in condition for allowance.

If the Examiner has any further comments or questions, he is invited to contact the undersigned representative for the applicant.

Respectfully submitted,

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